

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/007926 A (EGYT GYOGYSZERVEGYESZETI GYAR ; LEVAY GYOERGY (HU); GACSALYI ISTVAN (H) 30 January 2003 (2003-01-30) page 4	1-3, 5, 6, 9-22
X	WO 02/43726 A (ORION CORP ; MAEKI IKOLA OUTI (FI)) 6 June 2002 (2002-06-06) page 2-3	1-3, 9, 16, 18, 20, 22
Y	CAPONNETTO C ET AL: "Protective effect of cyproheptadine in a gerbil model of cerebral ischemia" ITALIAN JOURNAL OF NEUROLOGICAL SCIENCES, MASSON ITALIA EDITORI, MILAN, IT, vol. 12, 1991, pages 59-61, XP002979212 ISSN: 0392-0461 the whole document	1-22

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

6 October 2004

Date of mailing of the international search report

14/10/2004

Name and mailing address of the ISA

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Borst, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERENIJI ET AL: "EGYT-3886" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 15, no. 12, 1990, pages 1174-1175, XP000937796 ISSN: 0377-8282 the whole document	1-22
A	----- GACSALYI I ET AL: "DIFFERENT ANTAGONISTIC ACTIVITY OF DERAMCICLANE (EGIS-3886) ON PERIPHERAL AND CENTRAL 5-HT ₂ RECEPTORS" PHARMACEUTICAL AND PHARMACOLOGICAL LETTERS, SPRINGER INTERNATIONAL, BERLIN, DE, vol. 2, no. 6, 1996, pages 82-85, XP002902366 the whole document	1-22
A	----- ARMER R E: "INHIBITORS OF MAMMALIAN CENTRAL NERVOUS SYSTEM SELECTIVE AMINO ACIDTRANSPORTERS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 7, no. 2, 2000, pages 199-209, XP000937809 ISSN: 0929-8673 the whole document	1-22

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2004/000062

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT:
Although claims 16-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/HU2004/000062

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03007926	A	30-01-2003	HU 0103017 A2	28-07-2003
			CA 2453834 A1	30-01-2003
			CZ 20040060 A3	12-05-2004
			EP 1408940 A2	21-04-2004
			WO 03007926 A2	30-01-2003
			SK 312004 A3	08-06-2004
			US 2004171696 A1	02-09-2004
WO 0243726	A	06-06-2002	US 6335371 B1	01-01-2002
			AU 1833702 A	11-06-2002
			WO 0243726 A1	06-06-2002

PATENT COOPERATION TREATY

PCT

REC'D 11 OCT 2005

WIPO

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 17158 KB	FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/HU2004/000062	International filing date (day/month/year) 22.06.2004	Priority date (day/month/year) 23.06.2003	
International Patent Classification (IPC) or national classification and IPC A61K31/135, A61P25/28			
Applicant EGIS GY GYSZERGY R RT.			

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
 - a. ☐ sent to the applicant and to the International Bureau) a total of sheets, as follows:
 - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
 - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
 - b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand

21.01.2005

Date of completion of this report

10.10.2005

Name and mailing address of the international preliminary examining authority:

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**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/HU2004/000062

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-21 as originally filed

Claims, Numbers

1-22 as originally filed

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/HU2004/000062

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-22

because:

☒ the said international application, or the said claims Nos. 16-22 (no examination as to industrial applicability only) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. -

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/HU2004/000062

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4,7,8
	No: Claims	1-3,5,6,9-22
Inventive step (IS)	Yes: Claims	
	No: Claims	1-22
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

**Subject-matter excluded from international preliminary examination
(Rule 67.1(iv) PCT)**

Claims 16-22 are directed to a method for the treatment of the human or animal body by therapy and, thus, relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated under Section V with respect to industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Clarity (Article 6 PCT)

Present claim 3 is not clear, because in contrast to the teaching of the application it is directed to the preparation of pharmaceutical compositions having chronical neurodegenerative effect. Therefore, the search and the examination will be based in this respect on the preparation of pharmaceutical compositions for the treatment of chronical neurodegenerative disorders (cf. page 5).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: WO 03/007926 A (EGYT GYOGYSZERVEGYESZETI GYAR ; LEVAY GYOERGY (HU); GACSALYI ISTVAN (H) 30 January 2003 (2003-01-30)
- D2: WO 02/43726 A (ORION CORP ; MAEKI IKOLA OUTI (FI)) 6 June 2002 (2002-06-06)
- D3: CAPONNETTO C ET AL: "Protective effect of cyproheptadine in a gerbil model of cerebral ischemia" ITALIAN JOURNAL OF NEUROLOGICAL SCIENCES, MASSON ITALIA EDITORI, MILAN, IT, vol. 12, 1991, pages 59-61, XP002979212 ISSN: 0392-0461
- D4: BERENIJI ET AL: "EGYT-3886" DRUGS OF THE FUTURE, BARCELONA, ES, vol. 15, no. 12, 1990, pages 1174-1175, XP000937796 ISSN: 0377-8282
- D5: GACSALYI I ET AL: "DIFFERENT ANTAGONISTIC ACTIVITY OF DERAMCICLANE (EGIS-3886) ON PERIPHERAL AND CENTRAL 5-HT₂ RECEPTORS" PHARMACEUTICAL AND PHARMACOLOGICAL LETTERS, SPRINGER INTERNATIONAL, BERLIN, DE, vol. 2, no. 6, 1996, pages 82-85, XP002902366
- D6: ARMER R E: "INHIBITORS OF MAMMALIAN CENTRAL NERVOUS SYSTEM SELECTIVE AMINO

ACIDTRANSPORTERS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS
BV, BE, vol. 7, no. 2, 2000, pages 199-209, XP000937809 ISSN: 0929-8673

1. Novelty (Article 33(2) PCT)

- (i). Claim 1 on file is directed to the further medical use of compounds according to formula I for providing a neuroprotective effect. In second medical use claims the therapeutic indication can be defined either explicitly or, as in the present case, implicitly by way of a certain mechanism of action. The Applicant now alleges that the neuroprotective mechanism clearly distinguishes the subject-matter of claim 1 from therapeutic indications, such as dementia or Alzheimer's disease as disclosed with D1. The Applicant refers in this respect to diazepam-induced amnesia. While it may be true that this particular condition is not curable by a neuroprotective effect, it should be noted that D1 and D2 explicitly refer to dementia or Alzheimer's disease, which are caused by neurodegeneration and, hence curable by neuroprotection. Reference to the particular diseases mentioned in the description on file does not help as long as these therapeutic indication have not been made part of the claims.
 - (ii). Claim 2 on file is directed to the preparation of pharmaceutical compositions *suitable* for the treatment of certain conditions. Due to the term "suitable for" the therapeutic indications defined in claim 2 are not a technical feature per se and do not impart any limitations to the scope of the claim, as any composition comprising a compound of formula I prima facie is to be considered as suitable for the treatment of diseases defined in claim 2.
- 1.1. The subject-matter of present claims 1-3, 5, 6, 9-22 is not new in the light of D1. D1 (page 4) discloses deramciclane, derivatives thereof including N-desmethylderamciclane, and salts thereof including the fumarate salt for use in the treatment
- (i) of mental disability consequent on stroke
 - (ii) of Alzheimer disease and dementia.
- Thus, the use of deramciclane for achieving a neuroprotective effect was anticipated by therapeutic indication (i) above, whilst the use for the treatment of chronic neurodegenerative disorders was anticipated by therapeutic indication (ii) above.
- 1.2. The subject-matter of present claims 1-3, 9, 16, 18, 20, 22 is not new in the light of D2. D2 (page 2-3) discloses deramciclane and salts thereof including the fumarate salt

for use in the treatment of Alzheimer disease and dementia. The same reasoning applies as under item 1.1. above.

2. Inventive step (Article 33(3) PCT)

The subject-matter of claims 1-22 of the present application does not involve an inventive step in the light of D3 and D4.

It has been shown with the application on file that deramciclanc has antiischemic activity in a gerbil model of cerebral ischemia.

It was known from the closest prior art that several serotonin antagonists, in particular cyproheptadine, are effective in the same gerbil model.

The objective technical problem to be solved in the light of D3 was, therefore, to provide, apart from cyproheptadine, alternative therapeutic agents for the treatment of cerebral ischemia.

D4 disclosing that deramciclanc has 5-HT₂ affinity comparable to that of cyproheptadine suggests the use of deramciclanc for solving the above technical problem and, thus, to arrive at the invention according to the claims on file. The Applicant argues that according to Piera M J et al., referred to in the description of the application, the neuroprotective effect of deramciclanc does not follow from the effect exerted on the 5-HT system. Piera M J et al. report that the 5-HT_{2A/2C} antagonist ritanserin and ketanserin are not effective protectants of the gerbil hippocampus against ischaemic damage and conclude that 5-HT_{2A} receptors are not directly implicated in the pathogenesis of global cerebral ischaemia in this model.

Nevertheless, with D3 it has been shown that other 5-HT antagonists, such as cyproheptadine are effective in the same model and, hence, irrespective of whether the other 5-HT antagonists, such as ritanserin and ketanserin were not effective, it was obvious to try for further 5-HT antagonists, in particular for those, which display a 5-HT₂ affinity comparable to that of the effective compound cyproheptadine, ie for deramciclanc.

Conclusion

As long as the claims on file are not clearly delimited from the D1 and D2, for instance in terms of the therapeutic indication, and as long as it has not been shown why the combined teaching of D3 and D4 does not render obvious the invention according to the claims on file neither novelty nor inventive step can be

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

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acknowledged.